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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,297	VAN URK ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-56,58-92 and 94-113* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56, 58-92 and 94-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed February 9, 2004. Claims 54-113 were previously pending.

2. Applicants cancelled claims 57 and 93 and amended claims 54, 55, 58-61, 74, 76, 77, 79, 80, 82, 83, 86, 87, 90, 91, 102, 111 and 112. Claims 54-56, 58-92 and 94-113 are pending and will be examined.

3. Applicants' claim amendments and cancellations overcame the following: objection to claims 54, 74 and 102; rejection of claims 55, 57-60, 77, 80, 82-89, 91 and 112 under 35 U.S.C. 112, second paragraph; rejection of claims 57 and 93 under 35 U.S.C. 103(a) over Goodey et al. and Fisher et al. The rejections not mentioned here are maintained for reasons given in the "Response to Arguments" section below.

Specification

4. Applicants' amendments to the specification are accepted and overcome the objection from the previous office action.

Drawings

5. The drawings (Fig. 9-17) were received on February 9, 2004. These drawings are accepted.

Response to Arguments

6. Applicant's arguments filed February 9, 2004 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 54, 56, 57, 59-67, 69, 70, 71, 74-76, 78, 79, 81, 90, 92, 93, 95-102, 104-106, 109, 111 and 113 over Goodey et al. and Fisher et al., Applicants argue that:

a) Applicants' invention provides extremely pure albumin preparations, by utilizing negative mode CE.

b) There is no motivation to combine Goody et al. with Fisher et al., since neither provides extremely pure albumin, provided by Applicants' method, and Goodey et al. emphasizes positive mode CE.

c) Modifying a positive mode chromatography to become a negative mode is not acceptable. Applicants cite an example of using octanoate by Goodey et al. to elute albumin from CE matrix at pH 4.5-5.5 in a positive mode, whereas Applicants perform CE in a negative mode, using octanoate with pH between 5.0 and 6.0.

d) CE of Goodey et al. is performed at pH 4.0-5.0, whereas Applicants' amendments have a CE performed at pH 5.0-6.0. Fisher et al. teach performing CE in a negative mode at pH 4.5-4.9, therefore do not teach pH 5.0-6.0.

Regarding a) and b), it is noted that the features upon which applicant relies (i.e., extremely pure albumin) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding c), the combination of references does not rely on modifying the positive mode chromatography of Goodey et al. into a negative mode chromatography. Rather, as Applicants' method comprises the steps of CE chromatography in negative mode and AE chromatography, additional steps, included in either Goodey et al. or Fisher et al., can be included. As to the use of octanoate in either of the modes, Applicants do not claim using the octanoate to adjust the pH of the solution used for CE negative mode purification step.

Regarding d), Applicants confuse the ion exchange columns with which the pH range of 4.5-4.9 is used. As stated by Fisher et al. "an appropriate practical range for pH adjustments prior to cationic ion exchanger treatment is from 5.1 to about 5.5" (col. 4, lines 19-22). Fisher et al. teach

adjusting pH of the solution which flowed through the anion exchange column to 5.3 before contacting the solution with cation exchange column (col. 3, lines 57-65). To clarify the pH ranges appropriate for positive and negative mode purification, the following passage from Chang (EP 0 422 769 A1; page 2, lines 43-55; page 3, lines 1-5); cited in the previous office action) is presented below:

"The pI of a protein is the pH at which there is a net zero charge on the protein. The pI values of proteins, which are specific for a particular protein, vary over the whole spectrum of the pH range. By varying the pH of a solution, the charge on a particular protein can be manipulated and utilized for the purification of a desired protein from contaminating proteins. When the pH of the solution containing the selected protein equals its pI, the net charge on the protein is zero, and the protein will not bind to either an anion- or a cation-exchange column. When the pH of the protein solution is decreased to below the pI of the selected protein, there will be a net positive charge on the protein which increases as the pH decreases. Under these conditions, proteins with a net positive charge will bind to a cation-exchange resin. The strength of binding to the resin is dependent on the total charge on the protein, i.e., if the PH is just below the pI of the protein, there will only be a small positive charge on the protein, and the binding to a cation-exchange resin will be very weak. If the pH of the solution is far below the pI of the protein, there will be a large positive charge on the protein, and the binding, to a cation-exchange resin, will be strong. When there is a net positive charge on the protein, the protein will have no affinity for an anion-exchange resin. Conversely, as the pH of the protein solution is increased above the pI of the protein, by the addition of alkali, there will be a negative charge on the protein which increases as the pH increases. As a result of this negative charge, the protein will be able to bind to an anion-exchange resin. The

strength of the binding is dependent on the strength of the charge on the protein. A negatively-charged protein will have no affinity for a cation-exchange resin."

Therefore, since albumin has a pI of 5.0 (Fisher et al., col. 3, line 37), to perform CE in a negative mode with respect to albumin, i.e., albumin having a negative charge and not binding to the CE column, requires having pH of the albumin solution above 5.0, which is exactly what Fisher et al. teach.

The rejections are maintained.

B) Regarding the rejection of claims 55, 77, 80, 82-84, 86, 88, 91 and 112 over Goodey et al. and Fisher et al., further in view of Shaklai et al., Applicants argue that:

a) Neither Goodey et al. not Fisher et al. teach glycosylated albumin, and Goodey et al. do not mention glycosylated albumin, therefore the combination is not obvious.

b) The combination of references is not suggested by references themselves, since Goodey et al. do not mention a possibility of further purification steps, Fisher et al. disclose only three purification steps and contemplates a gel permeation step, which Applicants' invention does not include. Therefore there is no reason to eliminate Goodey et al. gel permeation step.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, the fact that Goodey et al. do not mention Fisher et al. or Shaklai et al. does not mean that one of ordinary skill in the art would not have been motivated to combine the teachings of these references. As pointed out by Applicants, both Fisher et al. and Shaklai et al. were available before publication of Goodey et al., therefore one of ordinary skill in the art would have been motivated by reasoning of Shaklai et al. to remove the

glycosylated albumin, since it is also one of the impurities, which both Goodey et al. and Fisher et al. are purifying out from the albumin solution.

The argument about the number and type of steps in Goodey et al. and Fisher et al. is irrelevant to the claimed invention, since Applicants claim methods comprising certain steps, which means other steps, such as the gel permeation step of Goodey et al. can also be included.

The rejection is maintained.

C) Regarding the rejection of claims 58 and 94 over Goodey et al. and Fisher et al., further in view of Curling, Applicants argue that:

a) Curling uses pH 4.8 and positive mode ion exchange chromatography, contrary to Applicants' pH 5.0-6.0 and negative mode CE.

b) The purity factor of 97% of Curling is well below the purity level acceptable to Goodey et al.

c) The product of Curling is unstable.

Regarding a), Applicants also use positive mode ion exchange chromatography in step (2) of claim 54, and, since the order of steps is not relevant in the claimed method, the method steps are equivalent.

Regarding b), the purity factor is not claimed by Applicants, therefore it is not relevant in the consideration of comparison with prior art.

Finally, regarding c), it is noted that the features upon which applicant relies (i.e., albumin stability) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The rejection is maintained.

D) Regarding the rejection of claims 68, 73, 103 and 108 over Goodey et al. and Fisher et al., further in view of Ohmura and Chang, Applicants argue that independent claims 54 and 90 are patentable over Goodey et al. and Fisher et al., therefore this rejection should be withdrawn. The arguments regarding rejection of claims 54 and 90 were addressed above.

The rejection is maintained.

E) Regarding the rejection of claims 72 and 107 over Goodey et al. and Fisher et al., further in view of Ohmura and Chang, Applicants argue that independent claims 54 and 90 are patentable over Goodey et al. and Fisher et al., therefore this rejection should be withdrawn. The arguments regarding rejection of claims 54 and 90 were addressed above.

The rejection is maintained.

F) Regarding the rejection of claims 83, 85, 87 and 89 over Goodey et al. and Fisher et al., further in view of Shaklai et al. and Chang, Applicants arguments follow the same line as arguments concerning the rejection of claims 55, 77, 80, 82-84, 86, 88, 91 and 112. The arguments regarding rejection of claims 55, 77, 80, 82-84, 86, 88, 91 and 112 were addressed above.

The rejection is maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 82 and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 82 and 84 are indefinite in claim 82. Claim 82 is indefinite over the recitation of "collecting the albumin-containing anion exchange flow through from step 0" in step (xii). There is no "step 0" in the preceding steps of the method.

Claim Interpretation

9. Before proceeding with art rejections meaning of some of the terms present in the claims, for which the definitions were not provided by Applicants, will be interpreted. "Chromatography in the negative mode with respect to albumin" is interpreted to mean that albumin is not adsorbed onto the chromatographic matrix and is recovered in the flow-through, and "chromatography in the positive mode with respect to albumin" is interpreted to mean that albumin is adsorbed onto the chromatographic matrix. The term "initial albumin solution" is interpreted as the albumin solution before any of the purification steps. The term "glycoconjugate" is interpreted as any glycosylated material, such as glycoproteins, glycopeptides, etc.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. A note regarding rejection of the claims in which the order of steps was reversed: reversal of steps is considered to be prima facie obvious (see MPEP 2144.04 IV C), therefore claims in which the only difference is reversal of steps will be rejected together, for example, claims 54-75 and 90-110, claims 76-78 and 79-81, claims (82, 84) and (86, 88), claims (83, 85 and 87, 89).

MPEP 2144.04 IV

C. Changes in Sequence of Adding Ingredients

Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.).

12. Claims 54, 56, 59-67, 69, 70, 71, 74-76, 78, 79, 81, 90, 92, 95-102, 104-106, 109-111 and 113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS), supported by Ohmura et al. (EP 0 570 916 A2; cited in the IDS) and Lindquist et al. (U.S. Patent No. 4,086,222; cited in the IDS).

A) Regarding claims 54, 76, 79, 90 and 111, Goodey et al. teach a process for purifying an albumin solution, the process comprising:

(1) subjecting the albumin solution to cation exchange (CE) chromatography in the positive mode with respect to albumin in order to yield an albumin-containing CE product (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines1-10);

(2) subjecting the albumin-containing CE product, with or without intervening purification step, to anion exchange (AE) chromatography to yield an albumin-containing AE product (Goodey et al. teach a process comprising CE and AE chromatography, with a possible steps of affinity chromatography (AC), ultrafiltration and gel permeation chromatography before AE chromatography; see page 2, lines 6-31; page 3, lines 1-16);

(3) placing the albumin-containing AE product, without further purification, into a final container for therapeutic use (Goodey et al. teach placing the purified albumin into a plurality of

vials (page 6, lines 28-30) and placing the albumin solution into a bulk product formulation vessel, followed by completing formulation by addition of pharmacetutically acceptable excipients (page 27, lines 20-22).)

Regarding claims 56 and 92, Goodey et al. teach CE step utilizing a matrix such as SP-Sepharose FF, SP-Spherosil, CM-Spepharose FF, CM-Cellulose, Se-Cellulose or S-Spherodex (page 1, lines 30, 31; page 2, line 1; page 21, lines 5, 6). Goodey et al. do not specifically teach sulfopropyl subsituents as cation exchangers. As evidenced by Ohmura et al., SP stands for a sulfoprpyl group, for example, SP-Sephadex is sulfopropyl-dextran (page 5, lines 37-40). Since Goodey et al. teach SP-Sepharose FF and SP-Spherosil, they teach sulfoprpyl groups as cation exchangers.

Regarding claims 59, 60 and 95, Goodey et al. teach initial albumin solution with octanoate concentration of 1-10 mM (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 61, 62, 78, 81, 96, 97, 109, 111 and 113, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

Regarding claims 63 and 98, Goodey et al. teach AE step utilizing a matrix such as DEAE-Spherodex, Q-Hyper D, DEAE-cellulose, QAE-cellulose, TMAE, DMAE, DEAE Fractogel or DEAE Sepharose FF (page 25, lines 12-14). Goodey et al. do not specifically teach dialkylaminoalkyl subsituents as anion exchangers. As evidenced by Ohmura et al., DEAE means diethylaminoethyl group (page 6, lines 11-15), which is a species of dialkylaminoalkyl groups (Lindquist et al., col. 3, lines 53-56). Therefore, since Goodey et al. teach DEAE-Spherodex, DEAE Fractogel or DEAE Sepharose FF, they teach dialkylaminoalkyl subsituents as anion exchangers.

Regarding claims 66 and 101, Goodey et al. teach that solution undergoing anion exchange chromatography has a conductivity of less than 4 mS/cm, namely, 2.5 $\pm$ 0.5 mS/cm (page 32, lines 1, 2).

Regarding claims 67 and 102, Goodey et al. teach AE step run in a positive mode with respect to albumin (page 25, lines 9-29).

Regarding claims 69 and 104, Goodey et al. teach ultrafiltration of albumin solution to a concentration between 20-120 g/L or 80-110 g/L before loading onto AE column (page 24, lines 20-24).

Regarding claims 70 and 105, Goodey et al. teach AE column equilibrated with a buffer with conductivity in the range of 1-4 mS/cm or 1.5-5 mS/cm (page 25, line 20; page 32, line 1).

Regarding claims 71 and 106, Goodey et al. teach elution of albumin from CE column with a solution of octanoate (page 31, lines 21-25), which has specific activity for albumin (page 2, lines 1-4). Goodey et al. do not teach elution of albumin from AE column using a solution of octanoate. However, they teach that pH of the eluting solution should be about 5.5, so that the binding of octanoate causes a significant overall charge difference (page 31, lines 23, 24). They also teach loading the eluate from the cation exchanger onto AE column equilibrated with a buffer of pH 5.5 (page 31, lines 27-29).

Regarding claim 74, Goodey et al. teach concentration of albumin prior to AE step (page 24, lines 20-24).

Regarding claims 75 and 110, Goodey et al. teach fermentation of yeast cells to produce recombinant albumin (page 10, lines 14-31; page 11-14; page 15, lines 1-9), primary separation of albumin from other cell components (page 15, lines 23-31).

Regarding claims 76 and 79, Goodey et al. teach the albumin-containing AE (or CE) product

being subjected to at least one step selected from the group consisting of buffer exchange; concentration; dilution; dialysis; diafiltration; pH-adjustment; treatment with a reducing agent; heating; cooling; and conditioning, before being placed into the final container (Goodey et al. teach concentration, diafiltration and formulation of purified albumin into a final product (page 26, lines 12-29; page 27).

B) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

C) Fisher et al. teach albumin purification using CE and AE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16).

Regarding claims 54, 76, 79, 90 and 111, Fisher et al. teach subjecting the albumin solution to cation exchange (CE) chromatography in the negative mode with respect to albumin in order to yield an albumin-containing CE product (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7). Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).

Regarding claims 64 and 99, Fisher et al. teach AE step run in a negative mode with respect to albumin (col. 2, lines 30-38; col. 3, lines 46-56; col. 4, lines 1-7).

Regarding claims 65 and 100, Fisher et al. teach that albumin solution, which undergoes CE chromatography has a pH of 5.1-5.5 (col. 2, line 32).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al.,

would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17). The teaching of Fisher et al. regarding the anion exchange purification therefore enhances the ability of Goodey et al. to obtain highly purified albumin therapeutic treatments (Goodey et al., page 1, lines 1-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have eluted albumin from AE column with a buffer containing a compound having a specific affinity for albumin. The motivation to do so would have been that albumin elution could be accomplished with more specificity and efficiency, since no other proteins bound to a compound with specific affinity for albumin.

13. Claims 55, 77, 80, 82, 84, 86, 88, 91 and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS), and further in view Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984).

A) Claim 55 is drawn to a process according to claim 54 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 77 is drawn to a process according to claim 76 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 80 is drawn to a process according to claim 79 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 91 is drawn to a process according to claim 90 wherein the initial albumin solution contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step. Claim 112 is drawn to a process according to claim 111 wherein the initial albumin solution

contains glycosylated albumin and the glycosylated albumin is bound during the cation exchange step.

B) Neither Goodey et al. nor Fisher et al. teach initial albumin solution containing glycosylated albumin and the glycosylated albumin being bound during the cation exchange step.

C) Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% and fatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach binding of glycosylated albumin peptides to cation exchange column (page 3813, third paragraph; Fig. 1).

D) Regarding claims 82 and 86, Goodey et al. teaches a process for purifying an albumin solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column

containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding claims 84 and 88, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

E) Goodey et al. do not teach albumin purification using CE or AE chromatography run in a negative mode with respect to albumin.

F) Fisher et al. teach albumin purification using CE and AE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16). Fisher et al. teach that the order of ion exchange steps is not critical (col. 2, lines 38-40).

Regarding claims 82 and 86, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7); Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).

(x) collecting the albumin-containing CE flow through (Fisher et al. teach collecting the fluid containing albumin after CE chromatography; col. 3, lines 64-66);

(xi) subjecting the albumin solution to AE chromatography in the negative mode with

respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with an AE exchange matrix to remove proteins having isoelectric points above that of albumin (col. 2, lines 23-30; col. 3, lines 46-56; col. 4, lines 1-7);

(xii) collecting the albumin-containing AE flow through (Fisher et al. teach collecting the fluid containing albumin after AE chromatography; col. 3, lines 54-56).

G) Neither Goodey et al. nor Fisher et al. teach affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates.

H) Regarding claims 82 and 86, Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% andfatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE and AE chromatography steps run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided

by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by CE chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

14. Claims 58 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) as applied to claims 54 and 90 above, and further in view of Curling ("Methods of Plasma Protein Fractionation", pp. 77-91, 1980; cited in the IDS).

A) Claim 58 is drawn to the method of claim 54 wherein the initial albumin solution has an albumin concentration of 10-250 g/L, and claim 94 is drawn to the method of claim 90 wherein the

initial albumin solution has an albumin concentration of 10-250 g/L.

B) Neither Goodey et al. nor Fisher et al. teach initial albumin solution has an albumin concentration of 10-250 g/L. Goodey et al. teach obtaining albumin from large-scale fermentation, with a fermenter the size of 4000 L (page 13, lines 20-23). They also teach that the expected yield of albumin is greater than 1.5 g/L of culture. Therefore, the total amount of albumin obtained from 4000 L would be at least 6000 g of albumin. They also teach that after pretreatment and centrifugation 75% of the albumin present id diluted culture is recovered, which would translate into at least 4500 g of albumin in a solution of unspecified volume, to be loaded onto an ion exchange column.

C) Curling teaches industrial scale purification of albumin on AE and CE columns, with 500 g of albumin in 16 L (about 31 g/L albumin) loaded onto the columns (Fig. 2, page 81, paragraphs 3-6; Table 1).

It would have been prima facie obvious to one of ordinary skill in the art to have used initial albumin concentrations of Curling (greater than 10 g/L) in the combined method of Goodey et al. and Fisher et al. The motivation to do so, provided by Curling, would have been that purification with this albumin concentration resulted in a 97% pure product (page 82, second paragraph).

15. Claims 68, 73, 103 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) as applied to claims 54, 67, 90 and 102 above, and further in view of Ohmura et al. (EP 0 570 916 A2; cited in the IDS) and Chang (EP 0 422 769 A1; cited in the IDS).

A) Claim 68 is drawn to a process according to claim 67 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 73 is drawn to the process according to claim 67 wherein the albumin is eluted in the anion exchange

step with a buffer of pH 6.0-8.0. Claim 103 is drawn to a process according to claim 102 wherein the albumin solution which undergoes positive mode anion exchange chromatography has a pH of 6.0-8.0, and claim 108 is drawn to the process according to claim 102 wherein the albumin is eluted in the anion exchange step with a buffer of pH 6.0-8.0.

B) Neither Goodey et al. nor Fisher et al. teach albumin solution which undergoes positive mode anion exchange chromatography with a pH of 6.0-8.0, or the albumin being eluted in the anion exchange step with a buffer of pH 6.0-8.0.

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8, and eluted from the column using buffer with the same pH range (page 6, lines 18-24). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Fisher et al. The motivation to do so, provided by Chang, would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

16. Claims 72 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) as applied to claims 54, 67, 71, 90, 102 and 106 above, and further in view of Ohmura et al. (EP 0 570 916 A2; cited in the IDS) and Chang (EP 0 422 769 A1; cited in the IDS).

A) Claim 72 is drawn to a process of claim 71 wherein the buffer comprises 20-90 mM

phosphoric acid salt, and claim 107 is drawn to a process of claim 106 wherein the buffer comprises 20-90 mM phosphoric acid salt.

B) Goodey et al. do not teach albumin elution buffer comprising 20-90 mM phosphoric acid salt. Fisher et al. teach a suitable eluent for a material absorbed on AE column being 0.1 M sodium phosphate (col. 4, lines 28-30).

C) Ohmura et al. teach purification of albumin comprising AE chromatography step run in a positive mode with respect to albumin (page 6, lines 21-24). They teach that albumin can be adsorbed onto AE column using a phosphate buffer of pH 6 to 8 and salt concentration of 0.001-0.05 M, and eluted from the column using buffer with the same pH range and salt concentration of 0.05 to 1 M (page 6, lines 18-24). They teach anion exchange column buffer of 50 mM phosphate (page 11, lines 49-51). Chang teaches albumin purification comprising a step of AE chromatography (Abstract). Chang teaches that at pH > 6.1 albumin becomes more readily bound to the anion exchange column (page 4, lines 31-33).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a buffer with a pH of 6.0-8.0 of Ohmura et al. in the combined albumin purification method of Goodey et al. and Fisher et al. The motivation to do so, provided by Chang, would have been that at pH > 6.1 albumin bound better to AE column than contaminating proteins (page 4, lines 31-33).

17. Claims 83, 85, 87 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodey et al. (WO 97/31947; cited in the IDS) in view of Fisher et al. (U.S. Patent No. 4,228,154; cited in the IDS) and Shaklai et al. (J. Biol. Chem., vol. 259, pp. 3812-3817, 1984), and further in view of Chang (EP 0 422 769 A1; cited in the IDS).

A) Regarding claims 83 and 87, Goodey et al. teaches a process for purifying an albumin

solution, the process comprising the steps of:

(i) subjecting an albumin solution to a CE chromatography step run in positive mode with respect to albumin (Goodey et al. teach CE chromatography of an albumin solution on cation exchanger; see page 1, lines 26-31; page 2, lines 1-10; page 21, lines 1-26);

(ii) collecting an albumin-containing CE eluate (Goodey et al. teach collecting 6.5 volumes of eluate; page 21, lines 26-28);

(iii) subjecting the CE eluate to an AE chromatography step run in a positive mode with respect to the albumin (Goodey et al. teach AE chromatography run in a positive mode with respect to albumin; page 25, lines 9-26);

(iv) collecting an albumin-containing AE eluate (Goodey et al. teach collecting albumin-containing eluate; page 3, lines 4-16; page 25, lines 27-29);

(v) subjecting the AE eluate to an affinity chromatography (AC) step run in positive mode with respect to the albumin (Goodey et al. teach AC chromatography of albumin on a column containing a matrix which specifically binds albumin, such as DBA (Delta Blue Agarose) matrix; page 22; page 23, lines 1-20);

(vi) collecting the albumin-containing AC eluate (Goodey et al. teach collecting the AC eluate; page 3, lines 4-16; page 23, lines 16-20).

Regarding steps (xi) and (xii) of claim 83 (or steps (ix) and (x) of claim 87), these are repeated steps (iii) and (iv). Goodey et al. do not specifically teach repeating AE step in a positive mode with respect to albumin.

Regarding claims 85 and 89, Goodey et al. teach adjusting the pH of albumin solution and conditioning of albumin solution by addition of octanoate salt prior to cation exchange step (page 3, lines 20-22; page 16, lines 9-11).

B) Goodey et al. do not teach albumin purification using CE chromatography run in a negative mode with respect to albumin.

C) Fisher et al. teach albumin purification using CE chromatography in a negative mode with respect to albumin (Abstract; col. 2, lines 12-16). Fisher et al. teach that the order of ion exchange steps is not critical (col. 2, lines 38-40).

Regarding claims 83 and 87, Fisher et al. teach a process for albumin purification (Abstract), the process comprising:

(ix) subjecting the albumin solution to CE chromatography in the negative mode with respect to albumin (Fisher et al. teach contacting the albumin solution to be purified with a CE exchange matrix to remove proteins having isoelectric points below that of albumin (col. 2, lines 23-30; col. 3, lines 57-63; col. 4, lines 1-7. Fisher et al. teach adjusting the pH of the albumin solution to between 5.1 and 5.5 before loading onto CE column (col. 3, lines 57-65; col. 4, lines 19-22).);

(x) collecting the albumin-containing CE flow through (Fisher et al. teach collecting the fluid containing albumin after CE chromatography; col. 3, lines 64-66);

D) Neither Goodey et al. nor Fisher et al. teach repeating AE chromoatography steps or affinity chromatography run in a negative mode with respect to albumin and in positive mode with respect to glyconjugates .

E) Regarding claims 83 and 87, Chang teaches repeating AE chromatography steps to remove contaminating proteins from albumin solution (Abstract; page 4, lines 17-39).

F) Shaklai et al. teach that 10% of albumin present in human plasma is glycosylated (Abstract). Glycosylated albumin has altered ligand binding properties: bilirubin binding is lower by 50% andfatty-acid binding is reduced 20-fold (Abstract; Fig. 4, Fig. 5, page 3814, the last

paragraph; page 3815). Shaklai et al. teach separation of glycosylated albumin (= glycoconjugate) from non-glycosylated albumin on a GlycoGel B affinity column, to which glycosylated albumin bound, and non-glycosylated albumin was collected in a flow through (page 3812, seventh paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to add the CE chromatography step run in a negative mode with respect to albumin of Fisher et al. to the albumin purification method of Goodey et al. The motivation to do so, provided by Fisher et al., would have been that using ion exchange in negative mode with respect to albumin maintained albumin in solution, and resulted in efficient albumin purification while minimizing potential alterations to albumin structure (col. 2, lines 4-17).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have removed glycosylated albumin by affinity chromatography of Shaklai et al. in the method of albumin purification by Goodey et al. and Fisher et al. The motivation to do so, provided by Shaklai et al., would have been that glycosylated albumin had impaired function of binding and transporting of fatty acids (Abstract; page 3816, the last paragraph) and that albumin glycosylation may contribute to long term diabetic complications (page 3812, second paragraph). Therefore, removing glycosylated albumin from albumin solution according to Shaklai et al. enhances the ability of Goodey et al. and Fisher et al. to obtain highly purified albumin for therapeutic treatments (Goodey et al., page 1, lines 1-25), without a danger of introducing into a patient an inactive protein which might also contribute to diabetic complications.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have repeated the AE steps in the albumin purification method of Goodey et al., Fisher et al. and Shaklai et al. according to Chang. The motivation to do so, provided by Chang, would

have been that repeating AE steps resulted in albumin purity of greater than 99% (page 4, lines 44-46).

18. No claims are allowed.

Conclusion

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
April 8, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER